said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver is repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

39. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver.

Please add the following new claims.

42. The method of claim 1 wherein said uPA gene encodes secreted uPA.

43. The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

44. The method of claim 15 wherein said uPA gene encodes secreted uPA.

45. The method of claim 25 wherein said uPA gene encodes secreted uPA.

46. The method of claim 37 wherein said uPA gene encodes secreted uPA.

47. The chimeric mouse model system of claim 38 wherein said uPA gene encodes secreted uPA.

48. The method of claim 39 wherein said uPA gene encodes secreted uPA.

REMARKS

This Amendment After Final Rejection places the claims in condition for allowance or, alternatively, simplifies issues for appeal. Accordingly, the Amendment should be entered by the Examiner.

The Applicants and the undersigned agent wish to extend their thanks for the courtesies extended by Examiners Paras and Priebe during the telephonic interview conducted on October 10, 2002. Reconsideration of this application is respectfully requested in view of the above amendments and the following remarks. The present claim amendments and remarks are believed to address the issues discussed with the Examiners in the interview.

I. Claim Status. By this Amendment, claims 1-48 are pending. A clean copy of the claims is enclosed for the Examiner's convenience.

(i) Amended Claims. Claims 1, 8, 15, 25, and 37-39 have been amended without prejudice or disclaimer and are drawn in relevant part to a chimeric mouse, e.g., "having a genome which comprises a urokinase-type plasminogen activator (uPA) gene " (see claim 1) or, more simply, a chimeric mouse comprising a "genomic uPA" gene (see, e.g., claim 15), wherein "expression" of the transgene causes liver degeneration.

Support for liver degeneration due to "expression" of a uPA transgene is found throughout the specification, e.g., at page 11, lines 2-6.

Support for amending claim 39 to recite an immunetolerant mouse "lacking functional B and T cells" is found in the specification in the Abstract, line 2 and at page 11, lines 1-2.

With reference to a chimeric mouse, the phrases "whose genome comprises a urokinase-type plasminogen activator (uPA) gene " and "genomic uPA" gene are synonymous in referring to a mouse comprising a uPA gene that has been integrated into its genome. The

specification provides implicit support for genomic uPA. One of ordinary skill in the art would understand that mice that are "hemizygous" and "homozygous" for the uPA transgene have respectively one or two copies of the uPA gene at a specified chromosomal locus. Furthermore, the specification sets forth that the uPA gene is transmissible from parents to offspring, and that crossing of hemizygous uPA mice gives rise to either hemizygous or homozygous progeny (see specification at page 11, lines 17-26 and Example 1, page 17, lines 17- 26.) The fact that the uPA gene is chromosomal (i.e., genomic) is implicit in the ability to transmit the uPA gene from parents to offspring and the observation that the transmitted uPA gene assorts among the progeny (i.e., crossing of hemizygous parents gives rise to both hemizygous and homozygous progeny.) Hence, the amendment of the claims to call, e.g., for a mouse "having a genome which comprises a urokinase-type plasminogen activator (uPA) gene" or a chimeric mouse comprising "genomic uPA" is supported by the specification. Accordingly, the amendments to claims 1, 8, 15, 25 and 37-39 do not add new matter to the application.

(ii) New Claims. Claims 42-48 have been added. These claims are directed in relevant part to a transgenic mouse whose liver undergoes degeneration due to expression of secreted uPA. New claims 42-48 recite subject matter that had previously been recited respectively in claims 1, 8, 15, 25 and 37-39, but which has been removed from those claims.

"Secreted uPA" is supported implicitly in the application and therefore does not constitute new matter. "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" MPEP 2163, Part I (*citing Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116, emphasis added). In the present case, one of ordinary skill in the art of molecular genetics would understand that

disclosure of a "uPA" gene without elaboration is understood to mean wild-type uPA. It is further well established that wild-type uPA is a secreted protein that functions in the plasma during the clotting process to convert plasminogen to plasmin, which in turn degrades fibrin clots (*see* Sandgren et al., (1986) Cell 66:245-256 at page 245, referencing Collen et al., (1987) *In* The Molecular Basis of Blood Diseases, G. Stamatoyannopoulos et al. (eds.) Philadelphia: W. B. Saunders Co.), pp. 662-688). ("Sandgren et al." is of record in the application, *see* paper no. 4, Information Disclosure Statement filed on October 1, 1999.) Hence, recitation of "uPA" in the specification without further elaboration would convey to one of ordinary skill in the art that inventors were, in fact, in possession of wild-type secreted uPA at the time the application was filed.

Further support for liver degeneration effected by expression of genomic uPA is also found in the specification in the citation to Sandgren et al., *supra* (reference 16 at page 3, line 23, *see* list of references at page 31) which is incorporated into the specification by reference in its entirety (*see* specification at page 1, lines 26-30.) Hence, at pages 3-4, bridging paragraph, the specification sets forth that:

> [A] hepatocyte-lethal phenotype has been discovered in urokinase-type plasminogen activator (uPA) transgenic mice and such mice have been shown to be capable of liver replacement with xenografted rat hepatocytes [citing Sandgren et al; additional citations omitted.] Such replacement of the mouse liver with xenogenic rat hepatocytes is facilitated in a uPA mouse because uPA transgene expresssion places these hepatocytes at a growth disadvantage compared with non-transgenic hepatocytes [citing Sandgren et al.]

The foregoing passage establishes that Applicants had possession of the methods of effecting liver degeneration through expression of a uPA transgene that are set forth in Sandgren et al. Sandgren et al. disclose liver degeneration in transgenic mice caused by expression of an Alb-uPA fusion construct that results in elevated plasma uPA and fatal

hemorrhaging in newborns (Summary; page 245, column 2, lines 25-28; page 247, column 1, line 6; page 249, Figure 4). Accordingly, the citation of Sandgren et al. clearly conveys to one of ordinary skill in the art that the inventors were in possession of methods of effecting liver degeneration by expression of secreted uPA at the time the application was filed.

Hence, the normal usage of "uPA" and citation and incorporation by reference of Sandgren et al. are sufficient to convey to one of ordinary skill in the art that the inventors were in possession of methods of causing liver degeneration through expression of secreted uPa. Accordingly, claims 42-48 do not add new matter to the application.

II. Claim rejections.

(i) Rejections under 35 U.S.C. § 112, first paragraph. Claims 1-41 have been rejected as containing subject matter not described in the application in such a way as to reasonably convey to one of ordinary skill in the art that the inventors were in possession of the claimed invention at the time the application was filed. The Examiner contends that "secreted uPA" constitutes new matter. In response, to expedite prosecution of the application, claims 1, 8, 15, 25 and 37-39 have been amended to delete "secreted [uPA]." Hence, without conceding the correctness of the Examiner's position, the rejection of claims 1-41 as containing new matter is believed to have been addressed and overcome. Accordingly, reconsideration of claims 1-41 and withdrawal of all rejections of such claims under 35 U.S.C. § 112, first paragraph is requested.

Applicants note the subject matter of "secreted uPA" that was deleted from claims 1, 8, 15, 25 and 37-39 has been set forth in new claims 39-48, respectively. As set forth above in Part I (ii), one of ordinary skill in the art would understand that the term "uPa" without further elaboration is synonymous with wild-type secreted uPA. The term "secreted uPA" is further supported by the incorporation by reference into the specification of Sandgren et al., *supra*.

Accordingly, the specification conveys to one of ordinary skill in the art that, as of the filing date of the application, the inventors were in possession of methods of effecting liver degeneration by expression of "secreted uPA," as claimed. MPEP 2163.02 Accordingly, Applicants assert that claims 42-48 do not raise any issues of written description. (*see* MPEP 2163.04, Part II., "If the whole record now demonstrates that the written description requirement is satisfied, do not repeat the rejection in the next Office action.") Allowance of claims 42-48 is requested.

Accordingly, the term "secreted uPA" being supported implicitly in the specification, claims 39-48 do not introduce new matter into the application.

(ii) Rejections under 35 U.S.C. § 102(e). Claims 1-5, 8-12, 15-21, 25-33 and 36-41 remain or are newly rejected as allegedly anticipated by Kay et al., U.S. Patent No. 5,980,886 ("Kay"). In response, without conceding the correctness of the rejections, claims 1, 8, 15, 25 and 37-39 have been amended to call for, e.g., a chimeric mouse "having a genome which comprises a urokinase-type plasminogen activator (uPA) gene," as suggested by the Examiner or, synonymously, a chimeric mouse comprising "genomic uPA." As set forth by the Examiner, Kay teaches away from using a transgenic mouse comprising a uPA transgene (*see* Final Office Action at pages 6-7, bridging paragraph). Hence, Kay fails to disclose or suggest a chimeric immunetolerant mouse having a genome comprising a urokinase-type plasminogen activator (uPA) gene, as defined in the present claims. Accordingly, the rejection of claims 1-5, 8-12, 15-21, 25-33 and 36-41 as anticipated by Kay is believed to have been addressed and over come. Reconsideration of claims 1-5, 8-12, 15-21, 25-33 and 36-41 and withdrawal of all rejections under 35 U.S.C. § 102 (e) is requested, accordingly.

For the reasons set forth above, Applicants submit that Kay does not anticipate claims 1-5, 8-12, 15-21, 25-33 and 36-41. Accordingly, Applicants respectfully request

reconsideration of claims 1-5, 8-12, 15-21, 25-33 and 36-41 and withdrawal of all rejections of these claims under 35 U.S.C. § 102 (e).

New dependent claims 42-48 depend respectively from base claims 1, 8, 15, 25 and 37-39. Dependent claims are not anticipated if the independent claims from which they depend are not anticipated. *In re Fine*, 837 F.2d 1071, 1076, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). In view of the conclusion that claims 1, 8, 15, 25 and 37-39 are not anticipated by Kay, the dependent claims 42-48 are also not anticipated by Kay. Furthermore, Kay fails to disclose or suggest the immunetolerant mouse of claims 42-48 which comprises a liver degenerated by expression of secreted uPA. For this reason additionally, Kay does not anticipate claims 42-48. Allowance of claims 42-48 is respectfully requested.

(iii) *Rejections under 35 U.S.C. § 103(a).* Claims 1-41 remain or have been newly rejected as allegedly obvious over Kay et al., U.S. Patent 5,980,886 ("Kay"), Alt et al., U.S. Patent 5,583,278 ("Alt") and Roggendorf et al., *Intervirology* 38:100-112, 1995 ("Roggendorf").

In response, without conceding the correctness of the rejections, claims 1, 8, 15, 25 and 37-39 have been amended to call for, e.g., a chimeric mouse "having a genome which comprises a urokinase-type plasminogen activator (uPA) gene," as suggested by the Examiner or, synonymously, a chimeric mouse comprising "genomic uPA." As set forth above and as conceded by the Examiner, Kay does not suggest a chimeric mouse whose genome comprises a urokinase-type plasminogen activator (uPA) gene.

Nor is the defect in the Kay cured by the other cited references.

Alt is concerned solely with construction of mice deficient in recombination activating genes (RAG genes) with improved SCID phenotypes.

Roggendorf is a general discussion of the woodchuck model for studying hepatitis B virus infection in man.

Neither of the references include any disclosure or suggestion regarding uPA-induced liver degeneration. Hence, neither Alt nor Roggendorf, either alone or combination with Kay, discloses or suggests that there would be any benefit of advantage in using a genomic uPA transgene to effect liver degeneration in an immunetolerant mouse for use as an acceptor for donor human hepatocytes.

For the reasons set forth above, Applicants submit that claims 1-41 are not obvious over Kay taken in view of Alt and Roggendorf. Accordingly, Applicants respectfully request reconsideration of claims 1-41 and withdrawal of the rejection of these claims under 35 U.S.C. § 103 (a).

III. Mouse Model for Hepatitis. The Examiner has asserted that claims directed to a mouse model for hepatitis do not recite any attributes of a model system for hepatitis and has suggested amending the relevant claims to call for the specific characteristics that make the claimed mouse a model system for hepatitis.

The Examiner's assertion is not well founded and is respectfully traversed. As Applicants discussed with the Examiner during the telephonic interview conducted October 10, 2002, the claimed chimeric mouse model system for hepatitis comprises degenerated liver that has been repopulated with xenogenic hepatocytes that are infected with a compatible mammalian hepatitis virus (claim 8) or which are a natural host for infection with one or more compatible hepatitis virus (claim 38). It is the repopulated mouse liver infected with or capable of being infected with hepatitis virus ***per se*** that is the specific characteristic suggested by Examiner. This is an attribute of this model system for hepatitis. That is, the repopulated liver *per se*, allows the

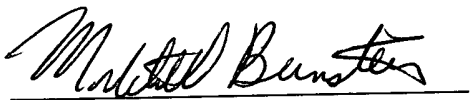
chimeric mouse to be a cost effective and adaptable small animal model for hepatitis virus infections of the liver and allows high numbers of animals to be tested in controlled environments (specification at page 4, lines 24-27). The repopulated liver *per se* allows for infection with hepatitis virus and testing the effectiveness of antiviral agents infected with hepatitis virus (*Id.* at page 5, lines 19-24). The repopulated liver infected with hepatitis virus *per se* develops hepatocellular carcinoma, thus allowing testing of agents that target developing cancers within the liver (*Id.* at page 5, lines 25-30 and page 13, lines 6-20). The repopulated liver *per se* also allows for toxicity testing of compounds towards the transplanted hepatocytes. And, the repopulated liver *per se* provides a model that may be manipulated genetically to test the effects of mutations on both the infecting virus and the recipient transplanted liver cells. In each of these examples, the ability of the chimeric mouse to function as a "model for hepatitis" inheres directly to the degenerated liver repopulated with xenogenic hepatocytes that are infected or are capable of being infected with one or more compatible hepatitis virus. Accordingly, the repopulated liver called for in the present claims is the attribute that makes the chimeric mouse a model system for hepatitis. Applicants assert accordingly that that no further features of the claimed mouse model system beyond the repopulated liver need be set forth in the claims.

CONCLUSION

Therefore, in view of the above amendments and remarks, reconsideration of this application is respectfully requested. Based on the preceding comments and amendments, the present claims are believed to be in condition for allowance and such action is earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charles E. ROGLER et al.

Serial No.: 09/344,189

Art Unit: 1632

Confirmation no.: 8764

Filed: June 24, 1999

Examiner: P. Paras, Jr.

For: **CHRONIC HEPATITIS VIRUS INFECTION AND CLONAL HEPATO-CELLULAR CARCINOMA IN MOUSE REPOPULATED LIVERS**

MARKK-UP TO RESPONSE UNDER 37 C.F.R. § 1.116

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

November 7, 2002

Sir:

The accompanying Amendment amends the subject application as follows.

IN THE CLAIMS

Claims 42-48 have been added.

Claims 1, 8, 15, 25 and 37-39 have been amended as follows:

1. (4X amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse [which has a degenerated liver due to the presence of a secreted urokinase-type plasminogen activator (uPA) and which is] lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus.

8. (4X amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to the presence in the genome of said mouse of a [secreted] urokinase-type plasminogen activator (uPA) gene, said degenerated liver [that is] being repopulated with transplanted xenogenic mammalian hepatocytes, said xenogenic mammalian hepatocytes infected with a compatible mammalian hepatitis virus.

15. (Thrice Amended) A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to [presence] expression of a [secreted] genomic urokinase-type plasminogen activator (uPA) gene, said degenerated liver being [that is] repopulated with transplanted xenogenic mammalian hepatocytes, and [wherein the] said xenogenic mammalian hepatocytes [are] being infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus.

25. (Thrice amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to [presence] expression of a [secreted] genomic urokinase-type plasminogen activator (uPA) that is repopulated with transplanted xenogenic mammalian hepatocytes, said [and wherein the] xenogenic mammalian hepatocytes [are] being infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma.

37. (Twice amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse [having a degenerated liver due to the presence of a secreted urokinase-type plasminogen activator (uPA) and] lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver.

38. (Twice amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse [deficient in] lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression [the presence] of a [secreted] urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver [that] is repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

39. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression [the presence] of a [secreted] urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver.

Pending Claims (as of November 7, 2002)

1. (4X amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus.

2. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

3. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

4. The method of claim 1, which comprises selecting the xenogenic mammalian hepatocytes from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

5. The method of claim 1, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

6. The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

7. The method of claim 6, wherein the xenogenic mammalian hepatocyte is from a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

8. (4X amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells having a degenerated liver parenchyma due to the presence in the genome of said mouse of a urokinase-type plasminogen activator (uPA) gene, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes, said xenogenic mammalian hepatocytes infected with a compatible mammalian hepatitis virus.

9. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

10. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulation.

11. The chimeric mouse model system of claim 8, wherein the xenogenic mammalian hepatocytes is a member selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

12. The chimeric mouse model system of claim 8, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

13. The chimeric mouse model system of claim 8, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and is homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

14. The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

15. (Thrice Amended) A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a genomic urokinase-type plasminogen activator (uPA) gene, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes, and said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus.

16. The method of claim 15, wherein the mammalian virus is at least one hepatitis virus.

17. The method of claim 15, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

18. The method of claim 15, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus prior to said transplanting.

19. The method of claim 16, which comprises infecting the xenogenic mammalian hepatocytes with the compatible mammalian virus following said repopulating step.

20. The method of claim 15, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

21. The method of claim 15, wherein the compatible mammalian virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

22. The method of claim 15, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

23. The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

24. The method of claim 15, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

25. (Thrice amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells which have degenerated liver parenchyma due to expression of a genomic urokinase-type plasminogen activator (uPA) that is repopulated with transplanted xenogenic mammalian hepatocytes, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma.

26. The method of claim 25, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

27. The method of claim 25, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

28. The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

29. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with a hepatitis virus prior to said transplantation step.

30. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting step.

31. The method of claim 25, which comprises infecting the xenogenic mammalian hepatocytes are infected with hepatitis virus following said repopulating step.

32. The method of claim 25, which comprises selecting the xenogenic mammalian hepatocyte from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

33. The method of claim 25, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

34. The method of claim 25, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for the urokinase-type plasminogen activator (uPA) transgene and homozygous for the Recombination Activation Gene 2 (RAG-2) knockout gene.

35. The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

36. The method of claim 25, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

37. (Twice amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver.

38. (Twice amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and

said degenerated liver is repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

39. (Amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse; and

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver.

40. The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

41. The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

42. The method of claim 1 wherein said uPA gene encodes secreted uPA.

43. The chimeric mouse model system of claim 8 wherein said uPA gene encodes secreted uPA.

44. The method of claim 15 wherein said uPA gene encodes secreted uPA.

45. The method of claim 25 wherein said uPA gene encodes secreted uPA.

46. The method of claim 37 wherein said uPA gene encodes secreted uPA.

47. The chimeric mouse model system of claim 38 wherein said uPA gene encodes secreted uPA.

48. The method of claim 39 wherein said uPA gene encodes secreted uPA.